REMARKS

Reconsideration of this application is requested in view of the amendments to the specification and the remarks presented herein.

The claims in the application are claims 24, 25, 27 to 30, 33 and 34, all other claims having been cancelled.

The specification has been amended to insert reference to the PCT application. Moreover, Applicants are submitting herewith an Abstract of Disclosure as required by the Examiner.

All of the claims were rejected under 35 USC 112, first paragraph, as being based on an application which is enabling for the administration of nomegesterol and estradiol in a continuous and uninterrupted fashion. The Examiner indicates that the specification does not provide enablement for "continuously without interruption" and does not limit how long it will be continuous.

Applicants vigorously traverse this ground of rejection since it is believed that the claims are clearly supported by the specification. The Examiner's attention is directed to lines 3 to 5 of page 4 of the application wherein it is clearly taught that the two compositions are administered "in a continuous or intermittent fashion". Lines 3 to 5 of page 4 have been clarified

since there was a misplacing of a comma and therefore, the specification clearly supports the fact that the compounds are administered continuously without interruption as can be seen from the example. With respect to the Examiner's query as to what is intended by "continuous without interruption", the Examiner's attention is directed to the Plunkett reissue patent cited during the prosecution. It can clearly be seen that this is an art recognized term. In claim 3 of the reissue application, it is stated "continuously and uninterruptedly administering the progesterone". Clearly, this is an art recognized term. "Continuous" means that the product is administered at least once daily and "uninterrupted" means that there is no break in the treatment and therefore, "continuous and uninterrupted administration" means that the products are administered at least once daily for the duration of the treatment which duration is determined by the doctor and the patient. Therefore, this is clearly an art recognized term and withdrawal of this ground of rejection is requested.

Further the same terms have also been used and clearly defined by Sitruk-War in the book the Menopause and Hormonal Replacement Therapy (Facts and Controversies) Ed Sitruk-Ware Regine and Utian W.H. Marcel Decker Inc. New York 1991.

The duration of the treatment is not part of Applicants' invention but, rather, the invention resides in the continuous

administration of estrogen and nomegesterol. The duration of the treatment is a case-by-case decision determined by the patient and/or her doctor depending on compliance of the patient and the evaluation of the benefits determined by the doctor. This does not depend upon the method of use but merely the doctor's observation as to the condition of the patient. Applicants' process has the advantage of preventing osteoporosis and cardiovascular diseases as can clearly be seen and the advantage of Applicants' method is that it can be used for very long periods and in some cases, at perpetuity. This can be seen by the prior art as taught by the Plunkett et al patent. Therefore, the claims are clearly supported by an enabling disclosure and withdrawal of this ground of rejection is requested.

In view of the amendments to the specification and the above remarks, it is believed that the claims clearly point out Applicants' patentable contribution and favorable reconsideration of the application is requested.

Respectfully submitted,
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CAM:ds
Enclosures

GEI-067

ABSTRACT OF THE DISCLOSURE

A method of treating estrogenic deficiencies in women while further avoiding the appearance of osteoporosis, withdrawal bleeding and cardiovascular diseases in post-menopausal women without any androgenic effect, and no deleterious effects on blood vessels comprising continuously without interruption administering to said women, a combination of 0.5 to 3 mg of an estrogenic compound and 1.5 to 3.75 mg of nomegestrol acetate.

--This application is a 371 of PCT/FR97/01792 filed October 8, 1997.--

HORMONAL COMPOSITION CONSISTING OF AN OESTROGEN COMPOUND AND OF A PROGESTATIONAL COMPOUND

The present invention relates to the field of therapeutic chemistry and more particularly to the field of hormonal pharmaceutical techniques.

A more precise subject of the invention is new pharmaceutical compositions formed by an estroprogestative combination with a view to the correction of estrogenic deficiencies in natural or artificial menopauses or in order to stop ovulation in women during their period of ovarian activity.

In particular a subject of the invention is an estroprogestative combination, characterized in that it is constituted by unit doses containing the combination of a progestative and an estrogen, the two components being present simultaneously in each medicinal dose.

This combination is intended to be administered by oral route.

As is known, the life expectancy of women has passed in less than a century from 50 to 80 years, whilst the average age for the onset of the menopause has remained unchanged. Therefore, women spend a third of their life in a state of estrogenic deficiency which is the origin of the increase in risk of osteoporosis and cardiovascular illnesses.

Sequential replacement treatment for the menopause cures the climateric symptomology and prevents osteoporosis and the onset of illnesses. It creates artificial cycles which are followed by a withdrawal bleeding. This therapeutic schema quite particularly suits women for whom the menopause is recent but it is not always well accepted in the long term, which in part explains the poorer observance of treatment (DRAPIER FAURE E.; Gynécologie. 1992, 43: 271-280).

In order to overcome this drawback, combined combinations have been perfected where the two components are taken simultaneously, the progestative having the effect of permanently opposing the proliferative action of the estrogen on the endometrium,

Pg. 4 of spec w/changes made.

post-menopausal women, or in stopping ovulation in women during their period of ovarian activity.

The compositions according to the invention based on nomegestrol and free or esterified estradiol or equine conjugated estrogens are administered in a continuous fashion or intermittent fashion from 21 to 25 days per month.

According to a particular implementation of the invention the compositions contain a quantity of nomegestrol acetate ranging form 1.5 to 3.75 mg and a quantity of free or esterified estradiol or equine conjugated estrogens ranging from 0.5 to 3 mg. Preferably, the optimal formulations contain 2.5 mg of nomegestrol acetate combined with : either 1.5 mg of free estradiol or 2 mg of estradiol ester or 0.625 mg of equine conjugated estrogens, per daily dose.

This combined administration method can have several therapeutic indications. In post-menopausal women, the estroprogestative combination is intended to compensate for the functional disorders brought about by hypoestrogenism of the menopause, while maintaining an atrophy of the endometrium and avoiding in a majority of them the appearance of withdrawal bleeding.

In women during the period of ovarian activity, young or in the years preceding the menopause, the cyclic administration of the hormonal combination is capable of stopping ovulation and of exercising a contraceptive effect insofar as it has been proved that nomegestrol is capable of stopping the ovulation peak of LH and FSH, starting from 1.25 mg/day (BAZIN B. et al, Effect of nomegestrol acetate, a new 19-norprogesterone derivative on pituitary ovarian function in women. Br. J. Obstet. Gynaecol., 1987, 94: 1199-1204). When the hormonal combination is given for a contraceptive purpose, the aim of nomegestrol acetate is to stop ovulation and for the estrogenic compound to compensate for hypoestrogenia and ensure a better control of the cycle.

A subject of the present invention is also a process for obtaining new pharmaceutical compositions.